Ifosfamide and Etoposide Chemotherapy in the Treatment of Recurrent/Refractory Rhabdomyosarcoma in Adults

SHINSUKE SASADA, MAKOTO KODAIRA, TATSUNORI SHIMOI, AKIHIKO SHIMOMURA, MAYU YUNOKAWA, KAN YONEMORI, CHIKAKO SHIMIZU, YASUHIRO FUJIWARA and KENJI TAMURA

Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

Abstract. *Background: No standard chemotherapy for adults with recurrent/refractory rhabdomyosarcoma (RMS) has yet been established. The present study aimed to assess the effect of ifosfamide and etoposide (IE) chemotherapy on previously treated RMS. Patients and Methods: Adults with recurrent/refractory RMS were treated with ifosfamide (1,800 g/m^2/day), etoposide (100 mg/m^2/day) and mesna (1,080 mg/m^2/day) for 5 days. The effect and toxicity were evaluated by chart review. Results: Fifteen patients, with a median age of 33 years (range=25-67 years), were treated with IE chemotherapy. A median of six cycles of chemotherapy were administered and an objective response was obtained in eight patients. The median progression-free survival was 5.2 months (95% confidence interval=2.3-6.7 months) and overall survival was 14.4 months (95% confidence interval=4.6-28.3 months). Toxicity greater than grade 3 was as follows: neutropenia in all patients, anemia in seven, thrombocytopenia in seven and febrile neutropenia in eight. Conclusion: IE chemotherapy could be an alternative optional treatment method in adults with recurrent/refractory RMS.*

Rhabdomyosarcoma (RMS) is a relatively rare cancer and usually occurs in children and adolescents. Although RMS represents more than 50% of all soft tissue sarcomas in children, its occurrence in adults is less than 3% (1, 2). Therefore, RMS studies have mainly been performed on pediatric patients and management of adult RMS is challenging.

In the recurrent and refractory settings, there are only a few reports on second-line chemotherapy, even for pediatric patients (3-5). Active chemotherapeutic agents for non-pleomorphic RMS include vincristine, d-actinomycin, cyclophosphamide, doxorubicin, ifosfamide, methotrexate and etoposide (6). Ifosfamide monotherapy led to a 22% overall response rate (ORR) in recurrent RMS (7). ORR for etoposide was 6% in pediatric solid malignancies (8). Ifosfamide and etoposide (IE) chemotherapy was found to be a highly active regimen, with an ORR of 69% for RMS in children and young adults (5). We investigated the effect and safety of IE chemotherapy in adults with recurrent/refractory RMS.

Correspondence to: Kenji Tamura, MD, Ph.D., Department of Breast and Medical Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-Ku, Tokyo, 104-0045, Japan. Tel: +81 335422511, Fax: +81 335453567, e-mail: ketamura@ncc.go.jp

Key Words: Rhabdomyosarcoma, adult, chemotherapy, ifosfamide, etoposide, response.

Patients and Methods

Patients. Among patients who received IE chemotherapy between April 2007 and April 2015 at the National Cancer Center Hospital, those who met the following eligibility criteria were included: age >20 years; histological diagnosis of RMS; disease recurrent/refractory to the previous chemotherapy; performance status 0-1; and with adequate cardiac, hepatic, renal and bone marrow function. The Institutional Review Board of the National Cancer Center Hospital approved the study (no. 2012-335). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

Treatment. Ifosfamide was administered at 1,800 g/m^2/day for 5 days and etoposide at 100 g/m^2/day for 5 days. Chemotherapy was repeated every 21 days for a maximum of six cycles. Mesna (360 mg/m^2, at 0 h, 4 h and 8 h after ifosfamide injection for 5 days) was infused for uroprotection. Granulocyte colony-stimulating factor (G-CSF) at 5 μg/kg/day was subcutaneously injected 24 h after completion of IE and continued until the neutrophil count reached 2,000/mm^3.

Assessment. Radiological examination, such as computed tomography, was performed every two or three cycles during treatment and every 3 to 6 months thereafter. The response was re-evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 (9). The adverse events were classified by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (10).

Table I. *Patient characteristics*.

Median age (range), years	33 (25-67)
Gender, n (%)	
Male	8 (53)
Female	7 (47)
PS (ECOG), n (%)	
0	4 (27)
1	11 (73)
Site of origin, n (%)	
Head and neck	13 (87)
Parameningeal	11 (73)
Genitourinary	1 (7)
Other	1 (7)
Histology, n (%)	
Embryonal	4 (27)
Alveolar	10 (67)
Pleomorphic	1 (7)
Prior chemotherapy, n (%)	
Responder	11 (73)
Non-responder	4 (27)
Prior irradiation, n (%)	
Presence	11 (73)
Absence	4 (27)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Statistical analysis. Summarized data are presented as numbers and percentages unless otherwise stated. Progression-free survival (PFS) and overall survival (OS) were analyzed by the Kaplan–Meier method using the log-rank test. The PFS was defined as the interval from the initial chemotherapy date to the first event (progression of disease or death from any cause). If no PFS events occurred, the last observation was censored. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (11).

Results

Fifteen patients were eligible and their characteristics are shown in Table I. The median age was 33 years. The most frequent primary site was the head and neck in 13/15 patients and alveolar histology was recognized in 10/15 patients. Prior chemotherapy was the same regimen [vincristine, d-actinomycin and cyclophosphamide (VAC)] and 13 patients showed a response.

The median number of cycles of IE chemotherapy was six, and eight out of 15 patients completed the planned six cycles. Two patients had a complete response and the ORR was 53% (Table II). The median PFS was 5.2 months (95% confidence interval=2.3-6.7 months) and the median OS was 14.4 months (95% confidence interval=4.6-28.3 months; Figure 1). In a univariate analysis, no predictive factors for PFS were identified (Table III).

Table II. *Treatment cycles and effect*.

	Number of patients
Cycles of treatment	
≤3	5
4	2
5	0
6	8
Total cycle number	68
Objective response	
CR	2
PR	6
SD	5
PD	2

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Toxicity data are summarized in Table IV. Hematological, gastrointestinal and hepatic events were common. Severe neutropenia was observed in all patients and severe anemia, thrombocytopenia and febrile neutropenia were frequent. There were no hemorrhagic cystitis or treatment-related death.

Discussion

The present study showed that IE chemotherapy was an active treatment for adults with recurrent/refractory RMS. Hematological toxicity was severe but was controlled by careful management.

The basis of chemotherapeutic regimens for pediatric RMS consists of VAC chemotherapy, which was developed by The Children's Oncology Group (12). Although some modifications, such as addition of doxorubicin, cisplatin and etoposide to VAC chemotherapy, have been examined, these did not lead to major improvements (13-15). In adult patients with RMS, there are few clinical trials and no standard chemotherapy regimen has yet been established. In addition, the prognosis of adult RMS was reportedly poorer than that for pediatric patients (16). However, a previous study indicated that multimodality protocol treatment of pediatric patients might improve survival in adult RMS (17). Therefore, we treated adult patients with RMS with the multimodality treatment containing VAC chemotherapy as the initial treatment.

The best treatment regimen for recurrent/refractory RMS has not yet been identified even for pediatric patients. Generally, chemotherapy after relapse was administered using agents that were not used in the initial treatment in order to avoid failure owing to acquired drug resistance (18). Pooled analysis of phase II window studies showed that

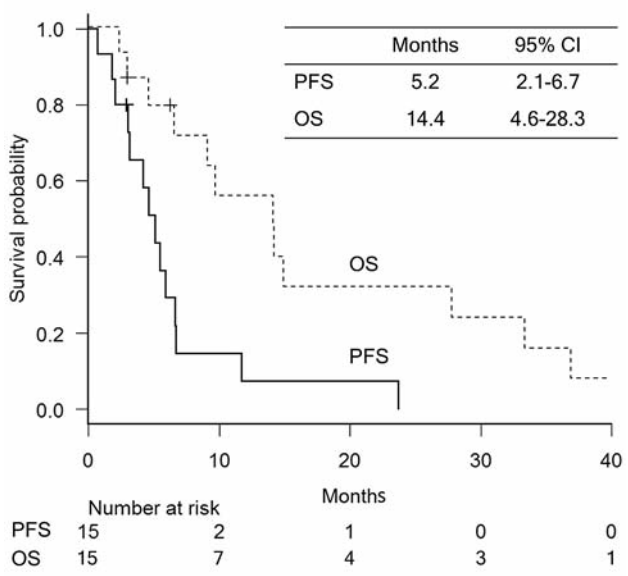

Figure 1. *Progression-free survival (PFS; solid line) and overall survival (OS; dotted line) by Kaplan–Meier method of 15 adult patients with recurrent/refractory rhabdomyosarcoma treated with ifosfamide/etoposide chemotherapy. CI, Confidence interval.*

Table III. *Univariate Cox proportional progression hazard model for predictors of progression-free survival.*

	HR	95% CI	*p*-Value
Age			
<33 Years	1		
≥33 Years	0.63	0.21-1.93	0.416
Gender			
Female	1		
Male	1.52	0.48-4.84	0.479
PS (ECOG)			
0	1		
1	2.91	0.64-13.3	0.168
Histology			
Embryonal	1		
Other	0.41	0.11-1.45	0.165
Prior chemotherapy			
Non-responder	1		
Responder	0.91	0.24-3.47	0.893

CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio, PS, performance status.

Table IV. *Toxicity.*

	Frequency, n (%)	
Toxicity	All grades	Grade ≥3
Leukopenia	15 (100)	15 (100)
Neutropenia	15 (100)	15 (100)
Anemia	15 (100)	7 (46.7)
Thrombocytopenia	14 (93.3)	7 (46.7)
Febrile neutropenia	8 (53.3)	8 (53.3)
Bilirubin increased	2 (13.3)	0 (0)
AST increased	8 (53.3)	0 (0)
ALT increased	9 (40.0)	1 (6.7)
Creatinine increased	3 (20.0)	0 (0)
Nausea	13 (86.7)	2 (13.3)
Vomiting	5 (33.3)	0 (0)
Appetite loss	10 (66.7)	1 (6.7)
Fatigue	12 (80.0)	2 (13.3)
Neurologic toxicity	0 (0)	0 (0)
Hemorrhagic cystitis	0 (0)	0 (0)

AST, Aspartate aminotransferase; ALT, alanine aminotransferase.

ifosfamide-based window therapy led to superior failure-free survival and that IE chemotherapy was promising in OS (19). The ORR for window IE chemotherapy was 79% (20). In the recurrent setting, IE chemotherapy gave an ORR of 69% in children and young adults with RMS (5). In this study, IE chemotherapy achieved an ORR of 53% for adults with recurrent/refractory RMS and was highly active when the agents had not been administered previously. As a stronger treatment, IE plus carboplatin re-induction therapy for recurrent/refractory sarcoma has been examined and the ORR was 51% for all sarcomas and 66% for RMS (4).

Hematological, gastrointestinal and hepatic toxicities were frequent with IE chemotherapy. Intermediate and severe (grade 3 more) events were mainly hematological. There were no instances of treatment-related death, hemorrhagic cystitis, or encephalopathy. More than 50% of patients completed the planned six cycles. The reasons for treatment discontinuation were progression of disease in four, toxicity in one and other reasons in two patients. IE chemotherapy for adult patients was well tolerated with supporting care such as administration of G-CSF, transfusion and antiemetic agents. However, this study has some limitations, such as its retrospective nature and a small sample size.

In conclusion, combination chemotherapy of ifosfamide and etoposide with uroprotection was effective and tolerable in adult patients with recurrent/refractory RMS. IE chemotherapy could be an optional treatment for recurrent/refractory adult RMS. Further studies are required to determine the efficacy of second-line chemotherapy for pretreated adult RMS.

Conflicts of Interest

None.

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